Specialty Conference

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Germ Cell Tumors of the Testes

Most malignant testicular neoplasms are of germ cell origin. They are divided into five basic types: seminomas, embryonal carcinomas, teratocarcinomas, adult teratomas and choriocarcinomas. Clinically they may present as an enlarging testicular mass, or with symptoms resulting from metastases or hormonal secretions. The treatment of choice for patients with seminomas is orchiectomy, followed by radiation therapy. This combination results in an 80 to 100 percent five-year survival rate in patients with nonmetastatic or locally metastatic disease. The treatment of nonseminomatous germ cell tumors is more controversial. An aggressive approach, however, with retroperitoneal lymph node dissection and adjuvant chemotherapy has resulted in an overall 78 percent survival rate. Several placental and fetal proteins are secreted by these tumors. Two of these, human chorionic gonadotropin and alpha-fetoprotein, have been shown to be useful for the diagnosis of these neoplasms, for following the disease activity during therapy and for detection of recurrences.

GLENN D. BRAUNSTEIN, MD:* Despite their relative infrequency, testicular neoplasms are among the most interesting tumors to cell biologists, pathologists and endocrinologists. Because approximately 95 percent of these tumors are of germ cell origin, the following discussion will focus on the pathologic, clinical and humoral manifestations of germ cell tumors of the testes.

Thirty years ago, the first widely accepted classification of these tumors was developed by Friedman and Moore.[1] It is therefore appropriate at this time to have Dr. Nathan B. Friedman discuss the classification and pathogenesis of testicular germ cell tumors.

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Pathology of Testicular Tumors

NATHAN B. FRIEDMAN, MD:† Most investigators[1-4] of germ cell tumors recognize that these neoplasms, despite their pleomorphism, manifest only a few basic histologic patterns. These patterns and their relative frequencies[5] are the seminomas (germinomas) (33 to 50 percent), embryonal carcinomas (20 to 33 percent), teratocarcinomas (10 to 33 percent), adult teratomas (10 percent) and choriocarcinomas (2 percent). The embryonal carcinomas, which are the least homogeneous group, include several distinct subtypes: trophoblastic, embryoid, endodermal sinus (yolk sac) and other subsets yet to be identified. The occurrence of all of these subtypes in complex combinations in some of the growths has obscured the basic simplicity of their interrelations. Most

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ABBREVIATIONS USED IN TEXT
AFP = alpha-fetoprotein
CEA = carcinoembryonic antigens
HCG = human chorionic gonadotropin

of these combinations can be classified by the term "teratocarcinoma."

There is general agreement that the adult teratomas result from undifferentiated elements developing into adult tissues just as the tissues and organs of the embryo emerge from embryonic epithelium during normal development. It is also accepted that choriocarcinoma develops as a manifestation of trophoblastic differentiation. The development of other extraembryonic tissues accounts for the formation of Teilum's endodermal sinus (yolk sac) carcinoma[2] and its infantile homologue.[6] The term "teratocarcinoma" was suggested to include growths that combined teratoid structures with carcinomatous ones, whether the latter were embryonal, seminomatous, trophoblastic (but short of true choriocarcinoma) or combinations of these types.

It is about the nature of the seminoma and its transformation into embryonal carcinoma that most of the controversy still exists. The seminoma cell was recognized as a specific cell type some time ago, but was thought to be a homologue of one of the elements of the seminiferous epithelium. The differences in the appearance and behavior of these monocellular growths from those of teratomas were obvious, despite the fact that the two neoplasms could coexist in the same testis, sometimes apart and sometimes intermingled. The gross and microscopic appearance of the seminoma, its sensitivity to irradiation and its good prognosis were also readily recognized. The specialized lymphoid or granulomatous stroma, which characterizes seminomas in any location, has led to the speculation that it might represent an immunologic reaction,[7] possibly a host-graft response. The granulomatous tissue rarely replaces the seminomatous so completely as to be misdiagnosed as granulomatous orchitis.[1]

Seminomatous cells are often present as individual elements within the surviving normal tubules at the margins of all types of germinal tumors. They represent the residua of the earliest stage in the development of the tumors and not a secondary invasion.

The spermatocytic seminoma,[8,9] which should be regarded as a specialized subtype, actually differentiates into homologues of the seminiferous epithelium; by contrast, the cells of the classical seminoma are homologous with primordial germ cells. The spermatocytoma is restricted to the postpuberal testis, whereas the seminoma can also occur in the ovary, thymus and pineal. Although the latter is associated with the usual array of teratoid tumors, the spermatocytoma is not. It represents differentiation toward the gamete, whereas the seminoma is totipotential.

Mostofi[4] considers anaplastic seminoma to be another subtype of the classical seminoma. The foci of embryonal carcinoma (which may be seen within seminomatous tissue[10] and within the transition zone in the occasional tumor combining seminoma and embryonal carcinoma) may signify transformation rather than classical anaplasia. There is an infrequent variant of seminoma in which giant syncytiotrophoblastic elements appear to emerge directly in the midst of purely seminomatous elements.[10-12]

With regard to trophoblast, it must be reemphasized that the "villi" in testicular choriocarcinoma are pseudovilli and lack the stromal and vascular cores of "true" chorionic villi.[10,13] Another unusual characteristic of trophoblastic tumors is the capacity for spontaneous regression leaving, at times, only a peculiar testicular cicatrix to mark the site of origin of a tumor whose metastases may have flourished and killed the patient.[10-12]

Pathogenesis of Germ Cell Tumors

To be worthwhile, a classification of tumors must be histogenetically sound, clear to oncologists as well as pathologists, and both therapeutically and prognostically useful. By minor modification and rearrangement of Mostofi's categories,[14] and by indicating the lines of development and differentiation between the various neoplastic entities, it is possible to construct a dynamic classification of testicular germ cell tumors (Figure 1).[15] This classification is supported by an overwhelming mass of evidence from a multitude of studies dealing with both human and animal tumors, from the disciplines of experimental pathology, embryology, genetics and electron microscopy.

Primordial Germ Cells

The existence of the primordial germ cells, their pregonadal origin and their migrations are well established.[16,17] There is little doubt as to their relationship to teratoid tumors.[10,18] The re-

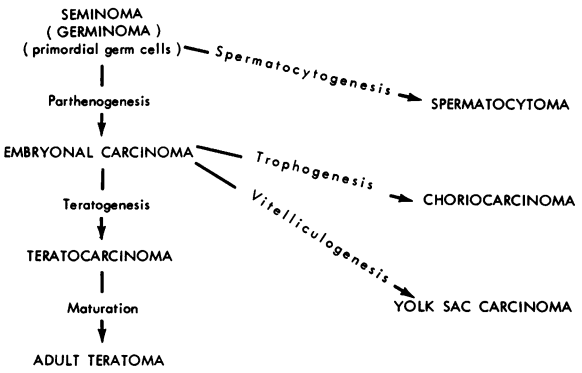

Figure 1.—Pathways of differentiation and transformation in testicular tumors. Oncogenesis recapitulates ontogenesis.[15]

semblance of seminoma cells to primordial germ cells in the normal human embryo is striking.[19] A high content of both alkaline phosphatase and glycogen, although not specific, is nevertheless common to both the cells of seminomas and to primordial germ cells.

Experimental interference with the extragonadal primordial germ cells results in a testis deficient in germ cells.[20-22] Genetic faults in C57 black mice homozygous at the W locus result not only in germ cell faults but also in anemia and pigmentary disturbances.[21,23] Stevens[24] showed that mice homozygotic for a comparable gene defect, and whose gonads had very few primordial germ cells, yielded only a 3 percent teratoma harvest as against 75 percent for the control mice whose gonads had normal numbers of primordial elements.

Metastases

The altered histologic patterns in metastases as compared with the morphologic pictures of the primary tumors are best explained in terms of progressive, metachronous or dissociated differentiation.[1,3,4]

Ovarian Tumors

Meyer,[25] recognizing the identity of the ovarian dysgerminoma with testicular seminoma, attributed the origin of both to a primitive cell before the stage of sexual differentiation. All of the teratoid types seen in the testis are encountered in the ovary, with the exception of the spermatocytic variant.[2] Another significant variation is the pronounced degree of differentiation seen in the ovarian teratomas as opposed to the less advanced level of tissue complexity attained by the testicular homologues.[1,11]

Extragonadal Tumors

Tumors of the pineal and diencephalon, as well as of the mediastinum and thymus, also manifest as seminomas, embryonal carcinomas, teratomas, choriocarcinomas and mixtures thereof.[11,26,27] Special subtypes, such as Teilum's yolk sac tumor, and the special stromal reactions, such as the pseudosarcoid granulomas, also occur,[7] but no spermatocytic seminomas are seen.

Experimental Teratoma Testis

The production of teratoid tumors in the intra-abdominal testes of roosters by injection of metallic salts has been successfully repeated many times.[28] The tumors begin as intratubular monocellular proliferation of embryonal elements at the edge of the testicular necrosis produced by the caustic metallic compounds. All stages from embryonal carcinoma to teratocarcinoma to teratoma can be observed.

Spontaneous Tumors in Animals

Teratomas appear in the testes of certain strains of mice; they begin as tiny intratubular cell complexes and culminate as teratocarcinomas, teratomas, choriocarcinomas and yolk sac tumors, which arise from embryonal carcinomas as in man.[29] It has even been possible to produce end-stage tumors by cloning single cells; the differentiation of teratomas from embryoid bodies can be readily observed by growing the tumor in the ascitic form.[10]

Ultrastructural Studies

Seminomas consist of a spectrum of cells including undifferentiated stem cells resembling primordial germ cells, spermatogonia, spermatocytes and embryonal carcinomatous elements, as well as elements reflecting abortive differentiation toward sperm cells.[9,10] Carcinogenesis involving the primordial cells or spermatogonia, present in prepubertal boys, could give rise to embryonal carcinoma and the teratoid series of tumors, but not to spermatocytic seminoma. In adults, where the complete series of stem cells is present, carcinogenesis could occasionally result in both the spermatocytoma and the teratoid series.

Genetic Studies

Linder, McCaw and Hecht[30] have found that ovarian teratomas are of germinal origin. By culturing cells from such tumors and studying chromosomal and enzymatic patterns, they showed

that the cell of origin must be a germ cell after the first meiotic division. In the case of the extragenital teratoid tumors they showed that the cell of origin is a nonmeiotic element, either a somatic cell or a misplaced germ cell.[31] Studies of sex chromatin[32,33] and karyotypes of teratoid neoplasms have shown "female" patterns in regular proportions of testicular growths. These data are compatible with both germ cell origin and a common ancestral element for seminomas and teratomas.[34]

Thus, the evidence from embryologic studies of the primordial germ cells, the patterns of metastasis, the homologous ovarian and extragonadal tumors, and spontaneous and experimentally induced or altered teratoid tumors in animals, as well as from ultrastructural studies and modern genetic studies, indicates that the various types of germ cell tumors are interrelated along the lines of normal embryogenesis (Figure 1).

Epidemiology

Incidence

STEPHEN A. SACKS, MD:* Tumors of the testicle approximate 1 to 2 percent of all male-related malignant neoplasms and account for 4 to 10 percent of genitourinary malignancies in men.[5,35] Testicular tumors make up the second most frequent malignant disease occurring in men between the ages of 20 and 34.[14]

Frequency and Geographic Distribution

The incidence of testicular tumors varies slightly among geographic areas in the United States, approximating 2 to 3 per 100,000 men per year.[14] This occurrence correlates well with the frequency reported from Canada, England and Wales,[14,35] but is significantly less than the occurrence reported from Denmark—that is, 4 to 6 per 100,000 men per year.[36]

Age Distribution

Testicular neoplasms have been recognized at all ages from the newborn through the ninth decade of life.[5] The peak incidence, however, occurs between ages 20 and 40.[5] Seminomas appear to develop later than other histologic types, with the average age of occurrence reported to be between 30 and 42 years. Embryonal carcinomas and teratocarcinomas tend to occur about five years earlier, and choriocarcinomas about ten years earlier, than seminomas.[5]

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Racial Differences

Significantly fewer germ cell tumors of the testicles occur in nonwhite than in white populations.[37] The incidence in blacks is a sixth to a tenth that of the white population. The greatest discrepancy in this occurrence appears in the younger age groups. These dramatic racial differences occur regardless of geographic locale and have been substantiated in American, European, Jamaican and African blacks.[37]

Such data tend to negate theories based upon latitude and mean annual temperatures as a basis for racial difference.[35] The incidence of testis tumors has also been noted to be significantly lower among Asian and Japanese.[4] It would be of critical epidemiological importance to determine the incidence of testicular tumors in nonwhite men with and without incomplete testicular descent.

Testicular Maldescent

The relationship between incomplete testicular descent and the subsequent development of germ cell tumors has long been recognized.[38] Some 4 to 12 percent of testicular neoplasms have been reported to occur in association with incomplete testicular descent, and the probability of malignant degeneration of a cryptorchid testicle is approximately 20 to 40 times greater than a normally descended testicle.[39] This relationship is not apparent in the development of testicular tumors in children.[40]

Malignant degeneration of the testicle may occur five to six times more frequently in abdominal maldescent than in inguinal maldescent,[41] and for a variety of reasons, the death rate related to malignant degeneration in the abdominal testicle appears to assume this same increase.[42] The observations that the risk of death from malignant degeneration exceeds the risk of anesthesia[43] or orchiectomy substantiates the rationale for removing the incompletely descended testicle after puberty. The development of testicular tumors in children in whom orchiopexy has been done after the age of six, but before the age of ten, is well-documented.[39,42] However, the role of hormonal or surgical orchiopexy before the age of six for the prevention of testicular malignancy has not been established.

Approximately 20 percent of cryptorchid-associated malignancy involves the contralateral, descended testicle.[39] This observation seems to support the theories of testicular dysgenesis as an

etiologic predeterminant of germinal neoplasms.[44] Finally, the ratio of right-sided to left-sided cryptorchidism and right-sided to left-sided neoplasm is approximately 5 to 4.[5] There is no satisfactory explanation for this phenomenon.

The Dysgenetic Testicle

The "dysgenetic" testicle, encountered most frequently in those maladies which we have termed "intersex," provides many clues regarding the cause of testicular tumorogenesis, but unfortunately no answers. One of the most curious of these disorders is the syndrome of testicular feminization, in which the gonad is a testicle, the karyotype is XY, but the phenotype is female. The testis is usually located in an inguinal hernia sac, and in 25 percent of the reported cases of patients over the age of 30 there were malignant germ cell tumors in these dysgenetic testicles.[45]

Bilateral Tumors

The synchronous and asynchronous occurrence of bilateral germ cell tumors has been clearly documented to exceed the limits of probability. It has been estimated that after the removal of one malignant testicle the chance of malignant degeneration in the remaining testicle is 700 times greater than for the general population. Almost all combinations of histological pattern have been reported.[46]

Familial Incidence

Numerous reports of the familial coincidence of germinal tumors of the testicle have shown that it occurs in monozygotic and dizygotic twins (with and without mirror-imaging), nontwin brothers (four in one report) and fathers and sons.[47-50] Synchronous occurrence is very rare, and different histopathology is frequent.

Trauma

A history of previous testicular trauma is frequently elicited or volunteered upon the diagnosis of a testicular tumor.[51] This relationship has been observed in approximately 8 to 25 percent of the cases reported. In addition to direct injury, there is often a history of mumps orchitis and atrophy, and occasionally a history suggestive of intermittent torsion.[52] No direct causal relationship has been established, however, between testicular trauma and the development of testicular tumors, and the prognosis is apparently not affected.[35]

Clinical Presentation

In 1779 Percival Pott made an extraordinarily perceptive assessment of the clinical presentation of tumors of the testicle: "Sometimes the first appearance is a mere simple enlargement and induration of the body of the testicle, void of pain, without inequality of surface, and producing no uneasiness nor inconvenience, except what is occasioned by its mere weight. And some few people are so fortunate to have it remain in this state for a considerable length of time, without visible or material alteration."[35] This is the clinical pattern regularly seen in modern urological practice,[52] and the "considerable length of time" alluded to by Pott between the first recognition of symptoms and the first examination by a physician usually exceeds five months.[51] Less frequently, there may be a rather sudden enlargement of a preexisting testicular mass, rapid enlargement associated with the signs and symptoms of inflammation, hemorrhage or infarction in a previously "normal" testicle.

Clinical presentation may be so subtle as to obscure an accurate initial diagnosis in 25 percent of patients. The onset of acute abdominal pain in a patient with a unilaterally descended testicle and a vacant contralateral inguinal canal should alert a physician to the possibility of torsion, hemorrhage, infarction or rupture of an intra-abdominal testicle. This clinical condition was first recognized in 1898 and is often confused with acute appendicitis.[51] Gynecomastia may be associated with testicular neoplasms but is not common as the presenting symptom. The presence of gynecomastia is usually bilateral and is not strictly correlated with any histologic pattern of disease. An evaluation of "adolescent gynecomastia" should include a thorough examination of the testicles. Approximately 10 percent of patients with testicular tumors present with symptoms referable to distant metastatic disease. These symptoms frequently include backache, skeletal pains, gastrointestinal complaints, inguinal adenopathy and neurological complaints.

Testicular tumors are often misdiagnosed as epididymitis and epididymo-orchitis. This error occurs in approximately 10 to 20 percent of patients in whom analysis is done retrospectively. If there is no funiculitis (inflammation of the spermatic cord), if the vas deferens on the involved side is not unusual and if there are no confirma-

tory signs of urinary tract infection, then tumor of the testicle must be strongly considered.

The diagnosis of simple hydrocele is made erroneously in 2 to 5 percent of testicular tumors. Frequently, a testicular tumor will have an associated hydrocele or may in itself be soft and cystic in consistency. Some authors have advocated the aspiration of a suspicious hydrocele with careful examination of the testicle immediately thereafter, although this practice could result in spread of tumor from the tunica vaginalis. Other less common differential considerations include inguinal hernia, hematoma, hematocele, torsion, spermatocele and varicocele, and rarely tuberculosis, gumma and sarcoidosis.[35,51]

When a testicular or intrascrotal mass presents a diagnostic dilemma, it is entirely advisable and appropriate to "explore" the lesion through an inguinal exposure. The spermatic cord may be readily secured at the internal inguinal ring, and the testicle with its fascial investment may be delivered intact into the area of the groin. The parietal layer of tunica vaginalis may then be opened and the diagnosis established. If the diagnosis is tumor, the testicle may be easily removed. Alternatively, if the lesion is benign the testicle may be easily returned to its hemiscrotal compartment without incurring significant morbidity. It is preferable to carry out this surgical procedure than to entertain the diagnosis of a testicular tumor and subject the patient to an unnecessarily long and uncertain follow-up.

Pretreatment Diagnostic Evaluation

RONALD W. THOMPSON, MD:* The accurate staging of patients with germ cell neoplasms of the testis requires an appreciation of the routes of dissemination, which can be local, lymphatic or hematogenous. Careful evaluation of the presenting signs and symptoms may also lend a clue to the location and size of metastasis. For example, lumbar pain may be an early sign of retroperitoneal involvement, or neck swelling and discomfort may be evidence of supraclavicular lymph node disease. Approximately 35 percent of these patients have metastasis when they are first seen, but the extent of metastasis will not be fully appreciated unless a consistent set of basic diagnostic evaluations is done.[52] The diagnostic procedures should include chest roentgenogram, intravenous pyelogram, bipedal lymphangiography, inferior venacavography (in selected cases), gonadotropin studies, and serum liver and renal function studies.

Before the advent of lymphangiography, routine studies were able to detect only 14 to 19 percent of patients with metastatic disease. With the development of this technique, Fein and Taber[53] were able to detect metastasis in 40 percent of their patients studied. Several authors have also favored testicular lymphangiography as a diagnostic procedure for evaluation of primary draining lymph nodes of the testis in the para-aortic region, which may not be opacified by foot lymphangiography.[54-56] From the practical point of view, however, by the time the patients have been referred for further diagnostic evaluation and treatment, they may have already had an orchiectomy, and the opportunity to do testicular lymphangiography is lost. Nevertheless, bipedal lymphangiography has shown an 87 percent overall accuracy in patients undergoing retroperitoneal lymph node dissection or in whom examination was done at autopsy. Despite its limitations, bipedal lymphangiography remains a viable staging tool.[52]

After these initial studies have been completed, the patient can be clinically staged. If the patient is stage A (tumor confined to the scrotum), the likelihood of additional testing showing the presence of other disease is quite low and not indicated. If there are suspicious findings, or clinical stage B (metastasis below the diaphragm) or stage C (metastasis above the diaphragm) is discovered, additional testing should be initiated. Whole lung tomography is valuable in detecting small, metastatic pulmonary nodules. Radionucleide studies are particularly helpful if symptoms indicate potential organ involvement. These include brain, bone, liver, and whole-body gallium scans. An additional procedure in stage B patients, particularly those in whom retroperitoneal node dissection is contemplated, is a biopsy of the left supraclavicular lymph node. Buck and associates[57] showed a 16 percent incidence of metastatic disease in this area in patients with stage B disease, and no evidence of metastases in patients with stage A disease.

Seminoma

Natural History

Seminomas comprise from 35 to 71 percent of primary germ cell tumors of the testes, the frequency depending on the hospital population of the series reported.[4] They occur more commonly

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in the fourth and fifth decades of life and no cases have been confirmed in infancy.[14] The right testis is more frequently involved than the left, and in about 8 percent of patients the tumor spreads beyond the capsule to the scrotal sac, the epididymis or the spermatic cord. Seminomas usually spread via the lymphatic system early in the disease and via the bloodstream later. Mostofi[14] noted that the most common metastatic sites at autopsy were the aortic and iliac nodes (71 percent), liver (54 percent), lung (57 percent), right kidney (6 percent), left kidney (37 percent), right adrenal (9 percent), left adrenal (35 percent), pancreas (21 percent), peritoneum (22 percent), pleura (17 percent) and mediastinal lymph nodes (17 percent).

TABLE 1.—*Five-Year Survival Rates of Patients with Seminomas of the Testis*

Reports	Patients* Number	Stage	Percent Survival
Doornbus et al[61]	79	A	94†
	48	B	81†
	5	C	60†
Saxena[63]	75	A & B	88
Maier et al[62]	181	A	91
	27	B	81
	11	C	18
Earle et al[60]	71	A	100
	27	B	85
	4	C	75
Ytredal and Bradfield[59]	71	A	98
	6	B	100

*All patients treated by orchiectomy and irradiation.
†Three years.

Radiation Techniques

Typical seminomas have an excellent prognosis, but the overall survival rate is dependent upon the stage at initial presentation. The most significant therapeutic factor of this neoplasm is its extreme sensitivity to ionizing irradiation. If all the seminoma could be encompassed in the treatment field, as little as 1,000 rads in two weeks can eradicate this tumor in the retroperitoneal lymph nodes.[58] Most authors, however, recommend higher doses to be delivered on megavoltage units. There is a considerable range of treatment schedules in different institutions, which have all reported similar success rates in managing this disease; they have utilized 2,000 to 4,000 rads in two to four weeks, depending on the stage of disease and the extent of involvement.

In stage A disease the ipsilateral inguinal-iliac and bilateral para-aortic lymph nodes are treated to the level of the crura of the diaphragm. The hemiscrotum should be included if a scrotal incision was made, if the tunica of the testis is involved, or if residual scrotal disease is suspected. Previous surgical procedures, such as herniorrhaphy or orchiopexy with its subsequent disruption of local lymphatics, dictate whether the contralateral inguinal-iliac lymph nodes should also be treated. Doses of 2,500 rads in three weeks to 3,500 rads in 3½ weeks are given without any significant sequelae. Irradiation above the diaphragm is generally not recommended, inasmuch as the incidence of subsequent failure with this therapy is almost nonexistent.[59-61]

In stage B disease, the same areas below the diaphragm as in stage A disease are irradiated. When bulky disease is present, however, the whole abdomen should be irradiated initially because of abdominal recurrences that have subsequently been found outside the usual treatment fields.[61] Usually about 2,000 rads are delivered in three weeks with partial kidney shielding, and then the nodal areas are boosted with an additional 1,000 to 2,000 rads through much reduced treatment fields. The role of chemotherapy in reducing this bulky disease has not been systematically investigated. As this disease usually spreads by the lymphatics in the early stages, most authors[60-63] recommend prophylactic mediastinal and supraclavicular lymph node irradiation from 2,000 to 3,500 rads in two to four weeks.

Therapy of stage C disease is determined individually. If disease is confined to lymph node structures, therapy is similar to that for stage B disease. Occasionally, if there is minimal pulmonary parenchymal disease, whole lung irradiation (1,500 rads in two weeks) with local boosts to the area of the nodule (additional 1,000 to 2,000 rads) may be successfully employed. If there is skeletal, visceral or bony disease, usually some combination of systemic chemotherapy and irradiation is recommended for maximal palliation.

Results of Therapy

Although not all authors use the same staging system, there are enough similarities to compare the results of therapy from various centers (Table 1).[59-62] In stage A, patients surviving five years vary from 91 to 100 percent. Stage B likewise has an excellent prognosis, with 81 to 100 percent of patients surviving five years. In the series of case studies (from the Armed Forces Institute of Pathology) by Nefzger and Mostofi,[64] 316 pa-

tients with all stages of seminoma were followed to 17 years after initial treatment; the survival rate in this series was 75 percent. These excellent results have been achieved in many institutions, with minimal morbidity from treatment.

Disseminated Disease

Because most patients with seminoma present in early stages A or B, and because the treatment with orchiectomy and irradiation is so successful (Table 1), the experience with advanced stage C disease or disseminated disease is limited. Seminomas, however, have shown sensitivity primarily to alkylating agents.[65] Combination chemotherapy programs have also been used with substantial objective regression rates.[66-68] Chemotherapy for bulky tumors or for advanced stage C patients, as part of the initial treatment plan rather than after a relapse, has not been explored but is to be encouraged. The five-year survival rate of stage C patients is as low as 18 percent and, obviously, calls for improvement.

Nonseminoma Germ Cell Tumors: Treatment and Prognosis

DONALD G. SKINNER, MD:* Treatment of nonseminomatous germ cell tumors of the testis remains controversial, despite recent literature reports of survival rates between 75 and 85 percent.[69-72] These improved statistics stem in part from meticulous lymph node dissection and judicious use of adjuvant modalities, including chemotherapy and radiation therapy.

Nevertheless, confusion exists regarding a rational approach to management, and some oncologists continue to believe that patients afflicted with these tumors are best managed by one modality, primarily radiation therapy.[73,74] Much of the difficulty stems from the following factors:

- The classification of nonseminomatous germinal tumors of the testis is not uniform nor is it understood, which makes it impossible to compare the results reported by various authors. Adoption of the Friedman and Moore[1] classification, based on biological behavior, greatly simplifies this problem; in a discussion of treatment, clinicians may therefore concern themselves with the overall management of the nonseminomatous group that includes all mixed forms. (Pure choriocarcinoma is an extremely rare tumor and will not be discussed in this presentation.)

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TABLE 2.—*Criteria for Pathologic Staging of Nonseminomatous Testis Tumors*

Stage	*Description*
A	Tumor confined to the scrotum. X-ray film of chest and intravenous pyelogram negative. No positive nodes on lymph node dissection.
B	Tumor metastases present below the diaphragm. X-ray film of chest and mediastinum normal.
B_1 ..	Gross or microscopic involvement of fewer than six well-encapsulated nodes, with no evidence of tumor extending through the node capsule and involving the retroperitoneal fat.
B_2 ..	Gross or microscopic involvement of more than six nodes, or tumor extending through the node capsule and involving the retroperitoneal fat.
C	Metastases present above the diaphragm.

- Inasmuch as patients with testis tumors are not numerous, it is difficult to develop a plan of management. There is, therefore, a tendency for one therapeutic modality to predominate, with not enough consideration given to a combined approach.
- It has only recently been shown that lymph node dissection can effectively remove the retroperitoneal nodes,[75] but indiscriminate use of postoperative radiation therapy in most surgical series has made it difficult to evaluate the contribution of lymphadenectomy to improved survival.
- Accurate staging is difficult unless surgical lymphadenectomy is done; moreover, many reports exclude advanced cases, thereby making biased patient selection an important factor in survival statistics.

We have recently reported[69] the results of treating 96 consecutive patients, with no exclusions, including 17 with stage C disease. Experience with these patients has led to a plan of management based on retroperitoneal lymph node dissection as the primary treatment modality, with use of adjuvant therapy as determined by the pathologic stage. Criteria for pathologic staging are listed in Table 2.

Patients who present with pulmonary metastases (stage C) or with clinical evidence of massive retroperitoneal disease are initially treated by a course of intensive inpatient chemotherapy (Table 3),[69] followed three weeks later by a five-week outpatient course of bleomycin (30 units given intramuscularly twice a week for five weeks, 300 units total) and vinblastine sulfate (10 mg given intravenously on day 1; 15 mg given intravenously on day 8, 20 mg given intravenously on day 21). After three weeks, retroperitoneal

TABLE 3.—*Initial Inpatient Course of Chemotherapy Given to Patients with Disseminated Disease (Stage C) or Clinical Evidence of Massive Retroperitoneal Disease*

Day	Drug	Dosage
1 ..	Actinomycin D	1.0 mg i.v. over 3 hr
	Cyclophosphomide (Cytoxan®)	2.0 mg/kg body weight i.v.
	Methotrexate	5.0 mg i.v.
2 ..	Repeat actinomycin D	
	Repeat Cytoxan	
3 ..	Repeat actinomycin D	
	Repeat Cytoxan	
	Repeat methotrexate	
4 ..	Repeat actinomycin D	
	Repeat Cytoxan	
	Vincristine	2.0 mg i.v.
	Prednisolone	20.0 mg p.o.*
5 ..	Repeat actinomycin D	
	Repeat Cytoxan	
	Repeat methotrexate	
	Repeat prednisolone	
6 ..	Actinomycin D	0.5 mg i.v.
	Repeat prednisolone	

*Prednisolone given to reduce toxicity.

TABLE 4.—*Survival for All Patients According to Pathologic Stage**

Stage	Number	Survival Percentage
A	39/43	91
B_1	12/14†	86
B_2	16/22	73
	67/79	85
C	8/17‡	47
Total	75/96	78

*From Skinner.[69]
†One death: operative mortality.
‡One postoperative suicide (18 months); no evidence of tumor at autopsy.

TABLE 5.—*Survival According to Cell Type**

Cell Type	Survival Number	Survival Percentage
Embryonal	28/36	78
Mixed	9/13	69
Teratocarcinoma	46/57†	81
Mixed	12/16	75
Choriocarcinoma	1/2	
Chorio Elements	10/14	71
Seminoma Elements	13/17	77

*From Skinner.[69]
†One operative mortality excluded.

lymph node dissection is done to remove bulk disease.

The retroperitoneal lymph node dissection is usually accomplished through the thoracoabdominal approach, which allows wedge resection of ipsilateral pulmonary metastases, a careful evaluation of the mediastinum and complete removal of all retroperitoneal metastatic disease. Dissection was done in all patients in this series, even for extensive tumor, and this occasionally included removal of the vena cava or an ipsilateral kidney.

Chemotherapy is considered the primary adjuvant, with actinomycin D as the basic drug. Dosage is based on the patient's weight and is given intravenously once a day for five days (each treatment course) (weight greater than 160 pounds: 5 mg over five days; 120 to 160 pounds: 4 mg over five days; less than 120 pounds: 3 mg over five days). Early in our investigations, chemotherapy was not generally used for patients in whom nodes were negative, but now it is our policy to initiate a course of actinomycin D during operation, continue it during the immediate postoperative period, and then repeat it once prophylactically.

In patients with pathologic stage B_1 or greater, cyclic chemotherapy with actinomycin D is recommended every two months for the first year and every three months for the second year.

If the primary tumor contains foci of choriocarcinoma, if choriocarcinomatous elements are present in metastases or if the patient has extensive retroperitoneal disease (stage B_2), at least one course of the combined vinblastine sulfate and bleomycin is substituted for the usual course of actinomycin D, given two to three months after lymphadenectomy.

Postoperative radiation therapy is reserved for those patients in whom there is extensive retroperitoneal disease (stage B_2). Beginning four to six weeks after lymph node dissection and postoperative chemotherapy, 4,500 rads are delivered to the retroperitoneum and ipsilateral iliac region. Four to six weeks after completion of radiation therapy, chemotherapy is resumed on a cyclic basis every two months for the first year and every three months for the second year.

In most patients with stage C disease, wedge resection of pulmonary metastases is done either at the time of lymph node dissection or through a formal thoracotomy three to six months after lymph node dissection. These patients receive a second full course of vinblastine sulfate and bleomycin after they have been rendered tumor-free by surgical operation; cyclic chemotherapy is continued with actinomycin D for a full two years after the last surgical procedure.

Survival for all patients in this series was 78 percent (Table 4).[69] For patients in whom disease was confined below the diaphragm, survival

was 85 percent. There was one postoperative death, representing a mortality of 1.3 percent. Table 5 lists survival according to cell type and supports our contention that the specific cell type or combination makes little difference in the total management plan or results of treatment.

Stage relates directly to the tumor-free interval and proves to be significant for survival; in no patient has there been a recurrence more than two years after lymphadenectomy. In stage A patients, the average time of tumor recurrence was 12 months, and there was no recurrence later than 22 months after lymphadenectomy. In stage B patients, average time of tumor recurrence was six months, with no recurrence later than 12 months postlymphadenectomy. In stage C patients, the average time of recurrence was three months, with a range of zero to nine months for recurrence. In no patient in stage C who was free of tumor for longer than nine months after lymphadenectomy and wedge resection of pulmonary metastases or thoracotomy was there a recurrence and none died of disease.

Within each stage, chemotherapy improved survival, and combined therapy that included radiation, surgical operation and chemotherapy resulted in notably improved survival for patients with advanced disease (Table 6).[69]

When surgical therapy fails, it is nearly always secondary to disseminated disease and the development of pulmonary metastases. In only one patient in our series with stage A or B disease did retroperitoneal recurrence develop; all other failures were due to pulmonary or disseminated disease. Based on this fact, it seems prudent to combine a systemic agent with known cytotoxicity against nonseminomatous tumors with hopes of sterilizing possible microscopic foci present beyond the field of surgical resection. Various cytotoxic drugs, in addition to actinomycin D, have been used as single agents or in combination, including methotrexate, chlorambucil, mithramycin, cyclophosphamide, adriamycin, vincristine and diaminodichloroplatinum; however, actinomycin D remains the primary drug that seems most effective against the nonseminomatous group of testis tumors.[76-82]

Our experience with the combination of vinblastine sulfate and bleomycin, supported by published reports by Samuels,[83] and Samuels, Holoye and Johnson,[84] leads us to believe that this combination is extremely active against this group of tumors; we recommend its use in all patients with extensive lesions or evidence of choriocarcinoma in the primary or metastatic tumor. However, because there is a limitation to the total cumulative dose of bleomycin, long-term therapy requires resumption of cyclic actinomycin D therapy.

Early in our studies, prophylactic chemotherapy was seldom used for patients with stage A or B_1 disease, but results indicated that in 18 percent of these patients pulmonary metastases developed and that they subsequently died of the disease. In other surgical series, the results are similar, regardless of whether postoperative radiation therapy to the retroperitoneum was employed. When failure occurs, it is almost always secondary to pulmonary metastases. Staubitz and colleagues[71] reported that pulmonary metastases developed in six of their 45 patients (13 percent) in whom nodes were negative. Consequently, it is our current practice to treat all stage A patients prophylactically with two courses of actinomycin D therapy; if elements of choriocarcinoma are present in the primary tumor, cyclic chemotherapy is continued for two years, in addition to one course of vinblastine sulfate and bleomycin. Whitmore[72] also supports this philosophy, and our current results indicate that survival can be improved from 82 to 93 percent for patients with minimal dis-

TABLE 6.—*Survival According to Adjuvant Therapy**

	Stages					
	A-B₁		*B₂*		*C*	
Adjuvant Therapy	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
None	18/22	82	1/1	100	1/1	100
Chemotherapy	28/30†	93	3/4	75	3/9	33
Radiation therapy	4/4	100	3/7	43	0/2	0
Chemotherapy + radiation	1/1	100	9/10	90	4/5‡	80
Totals	51/57	89	16/22	73	8/17	47

*From Skinner.[69]
†One death: operative mortality.
‡One patient committed suicide 18 months postoperatively; no tumor present at autopsy.

ease (stage A and B_1) treated in this manner (Table 5).[69]

We have shown that five-year survival now exceeds 90 percent for patients with negative nodes or minimal retroperitoneal metastases treated by lymph node dissection and chemotherapy. In this group, postoperative radiation therapy to the retroperitoneal area offers negligible tumor control, and resultant bone marrow toxicity further decreases patient tolerance to chemotherapy with effective cytotoxic drugs.

On the other hand, radiation therapy has been a helpful adjuvant in salvaging patients with advanced retroperitoneal metastases. It seems most effective in sterilizing microscopic residual tumors that undoubtedly remain after surgical resection of bulky, partially necrotic retroperitoneal masses. It has, therefore, been our policy to consider chemotherapy the primary adjuvant agent and to reserve radiation therapy for those patients with extensive retroperitoneal disease treated initially by surgical dissection (stage B_2). Mediastinal radiation therapy is not given unless mediastinal lymph node metastases are proven at the time of the thoracoabdominal dissection. A retrospective review of patients treated in this manner supports this concept and shows a greater than 80 percent survival for patients with stage B_2 or C disease treated with a combination of all three modalities (Table 6).[69]

Patients with stage C disease or those with clinical evidence of massive retroperitoneal disease continue to require individually tailored therapy. It is important to demonstrate a response to chemotherapy and reduce tumor bulk before beginning aggressive ablative therapy. If this approach is not considered, extensive retroperitoneal disease may be unresectable at surgical exploration; cure or long-term survival depends on removal of bulk retroperitoneal disease. Our results indicate that many patients in whom disease was previously thought to be incurable can be saved by an aggressive planned approach that combines therapeutic modalities.

Tumor Markers

DR. BRAUNSTEIN: Testicular germ cell tumors have been found to secrete a variety of placental and fetal proteins that may be responsible for some of the clinical manifestations of the disorder, such as gynecomastia. These proteins may also serve as useful tumor markers for the diagnosis of the tumor, for following the effects of therapy directed toward the tumor and for the detection of recurrences.

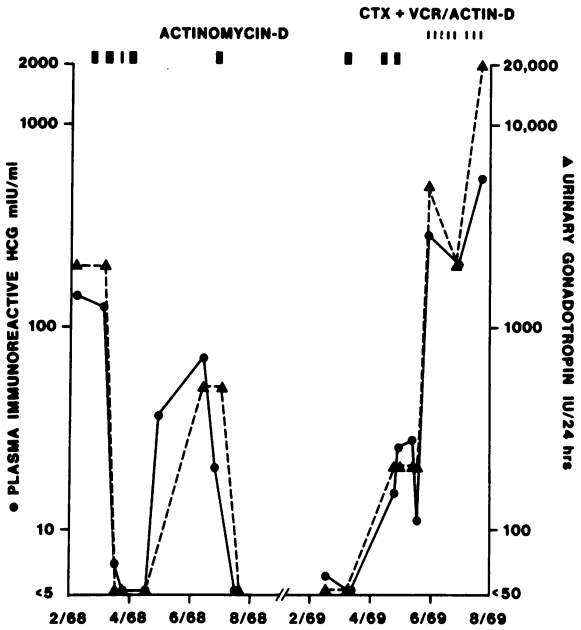

Figure 2.—Serum HCG levels measured by radioimmunoassay and total urinary gonadotropins measured by the mouse uterine weight method in a patient with metastatic teratocarcinoma of the testicle. Both the serum HCG and urinary gonadotropins paralleled the clinical course and other objective measures of remission and exacerbation.

Human Chorionic Gonadotropin

Human chorionic gonadotropin (HCG) is a glycoprotein hormone normally produced by the placental trophoblast during gestation. In 1927, Aschheim and Zondek[85] described the formation of hemorrhagic follicles in the ovaries of immature mice after injection of the urine of a pregnant woman. This bioassay was a measure of the ovarian-stimulating activity of HCG. In 1929, Zondek[86] observed a 30-year-old man with a metastatic testicular tumor whose urine produced a typical Aschheim-Zondek reaction. The patient's pituitary was free of the hormone. When tumor tissue was implanted into mice, the characteristic ovarian reaction resulted, implying that the tumor was a source of the HCG.[86] Since then, the measurement of HCG has become an essential part of evaluation in a patient with a suspected testicular tumor, and when present, this hormone has proved extremely useful for following tumor progression or regression (Figure 2). The source of the hormone appears primarily to be the trophoblastic elements in these tumors,[87] although in some HCG-secreting testicular tumors no trophoblastic elements could be identified.[88] The recent

identification of HCG (or an HCG-like substance) in the normal human testes,[89] suggests that some of the totipotential germ cells—which may be the precursors of germ-cell tumors—may have retained the capacity to secrete HCG. Neoplastic differentiation of these germ cells along nontrophoblastic lines may account for the HCG secretion by pure seminomas and embryonal-cell carcinomas.

Various methods for measuring HCG have been devised. Until recently, bioassays had been the procedure of choice. Although several biologic responses in many different species of animals have been described, the most widely used test measures the increase in the uterine weight in immature mice; the uterine enlargement is caused by the enhanced ovarian estrogen secretion that results from exposure to the HCG contained in the serum of urine of patients with trophoblastic neoplasms.[90] This procedure requires many mice, several days of injection of serum or urine in multiple dilutions, and concentration techniques when urine is the biological fluid in which HCG is measured. At low concentrations of HCG, the method is not specific, as the same biologic response may also be elicited from human pituitary luteinizing hormone, a glycoprotein with close structural similarity to HCG.

Both HCG and human luteinizing hormone are composed of two subunits, alpha and beta. The alpha subunit of these two hormones is similar, whereas the beta subunit of HCG contains 30 C-terminal aminoacid residues in excess of those present in the beta subunit of human luteinizing hormone.[91] Because of this structural similarity, radioimmunoassays, which were developed using antibodies directed against the intact human chorionic gonadotropin molecule, were unable to discriminate between HCG and luteinizing hormone. This specificity problem was resolved when a sensitive radioimmunoassay for HCG was developed that utilized an antiserum generated against the beta subunit of HCG.[92] This technique measured low levels of HCG in the presence of physiologic amounts of luteinizing hormone. Utilization of this assay has increased the detection of HCG in patients with germ cell tumors of the testes in comparison with the incidence as determined by bioassay (Table 7).[3,67,88,93-100]

The methods generally used by clinicians for measuring HCG are the commercial immunological urinary pregnancy heme-agglutination or latex-agglutination slide and tube tests. These tests have the advantages of convenience, low cost and rapidity, but *cannot* be used to exclude an HCG-secreting testicular tumor as a diagnostic consideration. Because of the above-mentioned immunologic cross-reaction between HCG and luteinizing hormone, when the intact molecules are used as immunogens, the sensitivity of these commercial tests is set at a level high enough to eliminate interference with the levels of luteinizing hormone reached during the midcycle surge of this hormone in menstruating women, or by the elevated levels found in postmenopausal women. Therefore, low levels of HCG will be missed if the urinary pregnancy tests are relied upon. Indeed, we have shown that between 33 and 44 percent of the patients with testicular tumors, in whom HCG was detected in the serum by the beta subunit radioimmunoassay, would not have had HCG detected if the commercial slide test had been solely relied upon (Table 8).

Measurement of HCG in patients with testicular tumors has been most useful in the follow-up of the effects of therapy. In many instances the HCG levels reflect the tumor burden, rising and falling in concert with other objective measurements of remission and exacerbation.[93,101] Exceptions are found, however, in patients with complex tumors consisting of different neoplastic elements (for example, teratocarcinoma) in whom the HCG

TABLE 7.—*Frequency of Human Chorionic Gonadotropin (HCG) Detection by Bioassay and Radioimmunoassay in Patients with Germ Cell Tumors of the Testes*

	Pathologic Classification							
	Seminoma		*Embryonal Carcinoma*		*Teratocarcinoma*		*Choriocarcinoma*	
Method	*Number*	*% Positive*	*Number*	*% Positive*	*Number*	*% Positive*	*Number*	*% Positive*
Bioassay*	283	19.9	154	30.5	193	32.2	39	82.1
Radioimmunoassay†								
Braunstein et al[88]	16	37.5	48	56	4	50	8	100
Cochran et al[100]	18	5.5	20	35	12	33	3	100

*Combined results of 10 series.[3,67,93-99]
†Two radioimmunoassay series listed separately because of a four-fold lower limit of detection in the method reported by Braunstein et al.[88]

TABLE 8.—*Serum Human Chorionic Gonadotropin (HCG) by Radioimmunoassay versus Expected Urinary Pregnancy Test Results in 84 Patients with Germ Cell Tumors of the Testes*

	Urinary Pregnancy Test		
Serum HCG	*% Negative*	*% Equivocal*	*% Positive*
Negative	36.9	0	0
Positive	33.3	10.7	19.1

levels may decrease despite tumor progression.[102] In these instances, radiation or chemotherapy may interfere with the synthesis of HCG by these tumors or may eliminate the HCG-secreting components, while not affecting the other neoplastic cell types. The persistence of HCG in the serum or urine of a patient with a testicular tumor is unequivocal evidence that the patient has residual disease.

The prognostic significance of the presence of HCG has been disputed. Several authors have stated that the presence of HCG in the serum or urine of a patient with a testicular neoplasm implies a poor prognosis.[94,103,104] These conclusions were based upon bioassay determination of HCG. Because of the specificity problems noted above, the levels of urinary gonadotropin had to be moderately elevated before the gonadotropin could be identified as HCG. Therefore, those patients in whom HCG is detected by bioassay may represent a group of patients with a larger tumor burden than those in whom HCG levels are undetectable by bioassay, but detectable by radioimmunoassay.

Alpha-Fetoprotein

In 1964, Tatarinov[105] described the presence of an $alpha_1$ globulin in the sera of human fetuses, in newborn infants and in patients with primary hepatomas. This protein is normally synthesized by the yolk sac, the gastrointestinal tract of the fetus, and by the fetal liver parenchymal cells.[106] Measurement of alpha-fetoprotein (AFP) has been used extensively for the diagnosis of hepatocellular carcinoma, in which elevated AFP levels are present in the blood of over 70 percent of the patients.[107] The association of AFP with testicular teratocarcinomas was reported simultaneously in 1967 by Masopust and associates[108] and Abelev and colleagues.[109] Since then, several investigators, using various methods for measuring AFP, have found elevated levels of this protein in 75 percent of the patients with teratocarcinoma or embryonal carcinoma of the testes (Table 9).[107,110-115] There was no evidence of elevated AFP in patients with pure seminomas or choriocarcinomas of the testicle. Several recent pathologic and immunofluorescence studies have shown that the cells responsible for AFP synthesis in testicular neoplasms are derivatives of the extraembryonic, primitive yolk sac.[111,116-118]

Alpha-fetoprotein is most sensitively measured by radioimmunoassay, which is also the procedure of choice for following the effects of therapy (Table 9).[107,109,115] As with HCG, the quantitative level of AFP correlates roughly with the tumor burden,[110,113,115] and changes in the level of AFP often—but not always—parallel other objective indices of changes in tumor growth.[102,115,119] As the site or origin of AFP differs from that of HCG, measurement of AFP should be part of the initial evaluation in all patients with testicular germ cell tumors (vide infra).

Carcinoembryonic Antigens

In 1965, Gold and Freedman[120] described a beta globulin that was present in colonic adenocarcinomata and fetal gastrointestinal tract. During the following ten years, many studies have elucidated the structural characteristics, heterogeneity, and normal and pathologic distribution of this substance.[121,122] Various methods of measurement have also been described.[123-125] There have been relatively few studies in which the sera of patients with testicular tumors have been exam-

TABLE 9.—*Results of Serum Alpha-Fetoprotein Measurements in Patients with Germ Cell Tumors of the Testes**

	Method†			
	Gel Diffusion		Radioimmunoassay Radioimmunodiffusion	
Cell Type	*Number*	*% Positive*	*Number*	*% Positive*
Seminoma	84	0	45	0
Teratocarcinoma and embryonal carcinoma	189	40.7	163	67.5
Teratocarcinoma after therapy	58	24.1	58	58.6

*Data from Waldmann and McIntire,[107] Abelev,[110] and Elgort et al.[115]
†Method sensitivities: Gel diffusion, 1-3 ug/ml; radioimmunoassay, 1 ng/ml; radioimmunodiffusion, 15 ng/ml.

ined for the presence of CEA (Table 10).[114,126,127] Although Wahren and Edsmyr[114] noted specific CEA immunofluorescent staining of a low percentage of cells in two of the four teratocarcinomas examined, the specific neoplastic element responsible for CEA production in germ cell tumors is unknown. The value of serial CEA measurements in following tumor progression or regression is currently unknown.

Other Antigens

Human placental lactogen (chorionic somatomammotropin) and placental alkaline phosphatase (Regan isoenzyme) are proteins normally synthesized by the placenta. Both have been shown to be secreted by some testicular germ cell tumors.[128-131] In the patients in whom tumors secrete placental lactogen, HCG is also produced.[129] The site of production of this material appears to be in the syncytiotrophoblastic and cytotrophoblastic elements in the tumors.[132] At present, not enough information is available regarding the value of serial measurements of these substances for evaluating tumor progression or regression.

Multiple Tumor Markers

Several groups of investigators have examined the sera of patients with testicular teratocarcinomas for the presence of more than one tumor antigen.[102,107,114,133,134] Braunstein, McIntire and Waldmann[102] described three cases of patients in whom tumors produced both HCG and AFP. Serial measurements of these proteins throughout the course of the patients' diseases showed discordant behavior of both proteins with each other. In two of the patients the HCG levels became undetectable despite persistence and growth of metastatic deposits. The AFP levels, however, remained elevated and paralleled the course of the patients' diseases. In the third patient, the AFP levels fell into the normal range, while the HCG titer correlated with progression of the tumor.

An expanded study of 101 patients with teratocarcinoma or embryonal carcinoma showed that in only 11 percent of the patients were findings negative for both HCG and AFP; in 58 percent both markers were present in sera; in 17 percent there were negative HCG levels with elevated AFP, and in 14 percent there was HCG production by the tumors with no elevation in the AFP levels.[107] Therefore, in 31 percent of the patients in this series there was elevation of only one of the two markers studied. Serial measurements of both HCG and AFP were carried out in 17 patients with disseminated disease, and discordance in the behavior of these proteins was again noted. Therefore, both HCG and AFP measurements should be made, at least initially, as part of the evaluation in a patient with testicular tumor. If levels of both proteins are elevated, then serial measurements of both of these substances should be carried out, as declining values of either one may not accurately reflect the status of the neoplastic process.[102,133]

Wahren and Edsmyr[114] measured both CEA and AFP in the sera of 32 patients with testicular teratocarcinomas. In 9 percent of the patients there were elevated levels of both CEA and AFP, in 47 percent neither antigen was elevated, in 25 percent there were elevated CEA levels with no elevation of AFP, while in 19 percent there were elevated AFP levels without a concomitant elevation of CEA.[114] Although no studies reported to date have examined serial CEA levels in patients with testicular tumors, it would seem prudent to measure this antigen as well as HCG and AFP in patients with testicular tumors.

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TABLE 10.—*Results of Serum or Plasma Carcinoembryonic Antigen Measurements in Patients with Germ Cell Tumors of the Testes*

		Pathologic Diagnosis			
		Seminoma		Teratocarcinoma	
Report	Year	Number	% Positive	Number	% Positive
Reynoso et al[126]	1972	9	44.4	12	50.0
Laurence et al[127]	1972	1	100.0	7	71.4
Wahren et al[114]	1974	23	4.4	32	34.4
Totals		33	18.2	51	43.1

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